

3rd International Ovarian Cancer Consensus Conference: outstanding issues for future consideration

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The process of consensus reflects an agreement upon one or more statements about a topic at a particular point in time. Subsequent to that time, the level of consensus and the nature of consensus may change. In this context, it is noted that this requires a dynamic process to remain current. The first Consensus Workshop on Ovarian Cancer was held in 1993 and the second in 1998. There has been a period of some 6 years since the last event. It is anticipated that as knowledge about ovarian cancer evolves, so will the need to realign consensus statements about the management of the disease process.

It is also acknowledged that any such process is unlikely to satisfactorily address all aspects of knowledge about the management of ovarian cancer. The 3rd International Ovarian Cancer Consensus Conference (OCCC) successfully focused on aspects of treatment relevant to the conduct of clinical trials. Although this was intended and appropriate, it was noted that this precluded appropriate consideration of the research and clinical elements of etiology, prevention, screening, early detection, diagnosis, supportive care and palliative care for those persons affected by ovarian cancer. Therefore, the framework for any subsequent conferences will have to consider these areas and define the scope of the process.

Thus, this manuscript will first summarize those specific questions that were generated through this OCCC which require further action before the next Conference. Secondly, there will be an identification of those new questions that emanated from this OCCC and may be considered for future consensus statements. Thirdly, there is a proposed agenda for a subsequent Conference subject to the ongoing changes in knowledge and practice. Finally, there is a brief discussion as to how this and earlier consensus workshops have affected current practice.

First, during the course of the OCCC it was recognized that there were a number of critical issues in the management of women with ovarian carcinoma that could and should be addressed prior to any subsequent consensus process. These proposed steps reflect discussion in the plenary sessions about specific questions. These steps are summarized in tabular format (Table 1). These items are identified with a specific responsible

cooperative group and a timeframe for action. It is expected that these items would be completed before a subsequent Conference.

The second component of this manuscript will seek to collate those new questions that emanated from this Conference and may be considered for future consensus statements. This is best considered in the context of a cancer control model.

A. Prevention and early detection

This topic was recognized as an area of intense interest during this Conference. This included the concept of identification of risk through molecular markers as well as the need for technological and genetic imaging techniques for early detection. The ability to conduct rapid proteomics screening for the purposes of early diagnosis is viewed as a critical issue for subsequent clinical trials.

B. Diagnosis

There is a need to conduct randomized prospective trials to validate biologic markers of disease and the impact on outcomes. This includes both known subpopulations at significant hereditary risk as well as less well-known groups. Molecular profiling through increased utilization of cooperative tumor banks has generated a considerable body of knowledge, but it is still not clear whether this is able to correlate with improved outcomes. Although much is known about the conventional histopathology of ovarian cancer, the specific entity of micropapillary ovarian tumors will require further study.

C. Methodology

Undoubtedly, the definition of end points in clinical trials that produce conclusions in a definitive but timely manner will remain of great interest. This is particularly relevant if one considers prevention, diagnostic and maintenance trials where traditional end points may not suffice. Even in therapeutic trials,

Table 1. Summary of proposed action steps

Proposed action	Lead group	Contact person	Timeframe
1. To undertake a systematic review of ovarian cancer treatment trials to assess shifts in progression-free relative to overall survival	MRC-UK	M. Palmar	2005
2. To confirm definition of terminology in ovarian cancer treatment trials	GCIG Harmonization Group	M. Bacon	2005
3. To conduct a literature review of patient perception of preferences for outcomes			
4. To review the characteristics of long-term survivors (i.e. >5 years) of prior ovarian cancer trials in advanced ovarian cancer	NCI-US	E. Trimble	2005
5. To conduct a meta-analysis of actual carboplatin dose using appropriate trials	MRC-UK	M. Palmar	2005
6. To establish a 'bank' of questions for consideration at next Ovarian Cancer Consensus Conference	GCIG	M. Bacon	2007
7. To establish a GCIG Working Group on the levels of evidence required to change the standard arm of clinical trials	GCIG	E. Avall-Lunquist	2005
8. To provide a definition and a validation tool of symptom control as a trial end point	NCI-C	A. Oza	2006
9. To conduct a meta-analysis of outcomes in the subset of clear cell and mucinous tumors	NCI-US	E. Trimble	2006
10. To identify the 'new' standard radiation therapy regimen for the treatment of women with advanced epithelial ovarian cancer	RTOG	M. Randall	2006
11. To define the role of PET scanning in future ovarian cancer clinical trials	NCI-US	E. Trimble	2005

stabilization of disease and control of symptoms could be considered as desirable primary outcomes for specific interventions being studied.

D. Treatment

The present OCCC did not intend to evaluate the role of surgery in the management of women with ovarian cancer. Yet, significant questions remain about the timing and extent of primary cytoreductive surgery and the specific role of secondary cytoreductive surgery. It is still not clear how best to apply detailed molecular pathology data including drug resistance/prognostic factors/molecular genetics to intelligently inform molecular targeted therapy amongst women with a diagnosis of ovarian cancer. There is increasing clinical adoption of neo-adjuvant therapy regimens without the supporting high quality evidence. This requires evaluation in a randomized trial setting. It is also apparent that there remains an asymmetry between available data, inferred knowledge and subsequent practice in the application of both dose-dense therapies and alternative administration routes for systemic therapy.

E. Follow-up and surveillance

The scheduling and nature of regular follow-up after completion of primary therapy for ovarian cancer has not been objectively determined. The duration of surveillance has been affected by therapies unable to allow long-term survivals. Furthermore, there is significant consideration about the establishment of standard second-line therapy regimens for those women who develop recurrent disease. This would impact front-line trials

directly, but also for more effective accrual into phase II and III second-line trials.

G. Survivorship

It is very positive that outcomes in the population of women with ovarian cancer have improved in the past few decades. However, this has created a number of new issues that require consideration. It is possible that much is to be learned from profiling those women who have long-term survivals following a diagnosis of ovarian cancer to better understand the disease. Furthermore, there are numerous issues to be considered amongst this population including quality of life, risk of second malignancies and next generation risk analysis.

H. Other issues

In addition to the clinical issues there are a number of related issues that must be given future consideration in the management of women with a diagnosis of ovarian cancer and the conduct of clinical trials. This includes regulatory issues within the Food and Drug Administration USA, pharmacoeconomic issues and the broader economic analysis. The need to harmonize regulatory issues around tumor banks is evident.

Discussion

With the rapid accumulation of new knowledge, the answers to many of these questions may quickly become apparent. Other areas may remain unresolved until after a subsequent workshop.

The third area for consideration is to identify those questions and issues that are anticipated to be of high priority at subsequent workshops and thus, provide a framework for an agenda. This futuristic consideration must allow for significant shifts in the knowledge about ovarian cancer. However, it is expected that subsequent workshops will still wish to consider four specific areas:

1. Early diagnosis. The benefit of early diagnosis has been identified but the specific mechanism to do so remains subject to investigation. This will include consideration of the role of proteomics as well as molecular markers. There should also be an assessment of the role of diagnostic imaging including PET scanning in women with ovarian cancer.
2. First-line therapies. This will likely remain as a focus of interest over the next decade and require ongoing review. This should include a consideration of the role of optimal radiation therapy both in first-line and salvage therapy.
3. Maintenance/consolidation. The question will likely remain as to whether one should consider novel therapies in this regard and what should the valid end points be in this setting.
4. Post-recurrence/progression therapy. This area will undoubtedly remain as a major issue. The question should consider treatment selection (as relates to prediction of response and resistance), appropriate surgery, measures of symptom control/quality of life, survivorship, end points. The issue of whether there should be a standard protocol for women with progressive disease after first-line therapy merits consideration.

The final area to be addressed is the impact that this and earlier consensus workshops have had on current practice. Although this issue is important to understand, it is one that is very difficult to quantify. If the intent is to influence the standard of practice, then one could consider that the shifts in 5-year survival rates as documented by FIGO are markers of this impact. During the period from 1988–2003, the 5-year survival rate for women diagnosed with stage III ovarian cancer has increased from 22.9% to a high of 49.2% (range 28.9% to 49.2%) [1]. Although numerically modest, this is a significant gain at a global level. However, there are multiple confounding factors in this correlation that may consider the relationship only as coincidental. If the intent of the consensus process is to provide support to the effective conduct of clinical trials, then the impact may be evaluated by a record of successful completion of international phase III trials in the population of women with a diagnosis of ovarian cancer. This is more readily quantified as since the previous consensus conference, there have been at least four randomized clinical trials completed assessing the first-line treatment of women with a diagnosis of advanced ovarian cancer that include accrual from more than one national

cooperative clinical trials group. In aggregate form, these trials and others have confirmed the role of a platinum compound with a taxane as standard therapy for women with ovarian cancer, recognized the option of single-agent carboplatin as a standard therapy and demonstrated the lack of benefit of an anthracycline to the above-mentioned regimens [2–6]. This may be viewed as a marker of positive impact on the global consensus process. However, it is important that future consensus workshops have included a process of evaluation in order to effectively measure the impact of this process on the burden of ovarian cancer.

Additionally, in considering the consensus process, it is apparent that the generation of new data so frequently presented in the setting of publications and/or meetings does not necessarily lead to better information. Furthermore, it is even less often that better information promotes new knowledge or practices. As new data become available, they must be considered in the context of how this might be effectively adopted into practice.

Future international consensus workshops on the treatment of women with ovarian cancer should consider the impact of previous workshops on the outcome of women affected by ovarian cancer. The relevant questions must be derived from a direct correlation of the issues with the desired outcomes and an opportunity created for discussion and consensus.

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